**Gompertz-Matsui model for HCV kinetics**

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**Gompertzian growth model for HCV kinetics**

When a biological growth obeys an exponential growth, its slope of the logarithmic translated data becomes straight. This relationship is expressed as follows:

\[
\frac{d\ln G(t)}{dt} = A_0
\]

Where \( \ln G(t) \) is the natural logarithm of the biological growth \( G(t) \) and \( A_0 \) is a positive slope.

It has been claimed that Gompertzian growth is representative of all biological growth. In Gompertzian growth, it is observed experimentally that an initial slope \( A_0 \) gradually decreases with time \( e^{-kt} \) times. This relationship is expressed as follows:

\[
A_0 e^{-kt} = k(\ln G_{max} - \ln G(t))
\]

Figure 1. Gompertzian growth curve and its slope

\[
\ln G(t) = \ln G_{max} - \frac{A_0}{k} e^{-kt}
\]

Gompertzian model reveals a logarithmic-transformed growth curve as follows; \( \ln G(t) = \ln G_{max} - \frac{A_0}{k} e^{-kt} \). Slope of \( \ln G(t) = A_0 e^{-kt} \) is \( k(\ln G_{max} - \ln G(t)) \).

**HCV decline curve by anti-viral therapy**

We hypothesized that HCV growth obeys Gompertzian function. If decay of HCV by anti-viral therapy causes an exponential decay, we should take into account the Gompertzian effect, that is, the smaller the viral load, the steeper is the slope of \( \ln G(t) \). Therefore, it is expected that decline curve will converge to a certain value, where decay by anti-viral therapy is equivalent to HCV replication. When \(-D_0\) is defined as an initial slope of exponential decay by anti-viral therapy, HCV decay \( H(t) \) is affected by replication force of HCV \( (k(\ln G_{max} - \ln H(t))) \). This relationship is expressed as follows:

\[
\frac{d\ln H(t)}{dt} = -D_0 + k(\ln G_{max} - \ln H(t))
\]

Where \( \ln H(t) \) is the natural logarithm of decline curve. (Figure 2)

Figure 2. HCV decline curve by anti-viral therapy

\[
\begin{align*}
\text{slope}=0 & \rightarrow Z = 3 \\
\text{slope}=1 & \rightarrow Z = 2 \\
\text{slope}=2 & \rightarrow Z = 1 \\
\text{slope}=3 & \rightarrow Z = 0 \\
\text{slope}=3+1 & \rightarrow Z = -1 \\
\text{slope}=3+2 & \rightarrow Z = -2 \\
\text{slope}=3+3 & \rightarrow Z = -3
\end{align*}
\]

The author proposed that the growth of HCV follows Gompertzian curve and anti-viral therapy causes exponential decay. The smaller the viral amount, the more is the driving force for replication due to Gompertzian function. Reduction curve will converge to the same level as the tangent slope of \( D_0 \), because at that level, the reduction force by anti-viral therapy is equivalent to the driving force for replication.

We rewrite the above equation as:

\[
-Z_0 + k(\ln G_{max} - \ln H(t)) = Z
\]

The derivative of the above equation is as follows:

\[
-k \frac{d\ln H(t)}{dt} = \frac{dZ}{dt}
\]

Because

\[
\frac{dZ}{dt} = -kZ
\]
\[ \int \frac{1}{Z} dZ = -k \int dt \]

\[ \ln Z = -kt + C \]

Where C is a constant.

\[ Z = e^{-kt} \cdot C = e^C e^{-kt} \]

When \( t = 0 \), slope is \(-D_0\), therefore \( e^C = D_0 \) and,

\[ \frac{d \ln H(t)}{dt} = -D_0 e^{-kt} \]

\[ -D_0 e^{-kt} = D_0 + k(\ln G_{\text{max}} - \ln H(t)) \]

\[ \therefore \ln H(t) = \ln G_{\text{max}} + \frac{D_0}{k} e^{-kt} \]

How to calculate \( k \) and \( D_0 \) values from actual data?

When HCV decay curve is expressed as

\[ \ln H(t) = \ln G_{\text{max}} - \frac{D_0}{k} + \frac{D_0}{k} e^{-kt} \]

the relationship between \( \ln H(t+s) \) and \( \ln H(t) \) is as follows:

\[ \ln H(t + s) = a + b \cdot \ln H(t) \]

Where \( s \) is a constant time interval. \( a \) and \( b \) are also constant. (Figure 3)

Figure 3. The relationship between \( \ln H(t+s) \) and \( \ln H(t) \)

When the measured values are expressed as

\[ \ln H(t) = \ln G_{\text{max}} - \frac{D_0}{k} + \frac{D_0}{k} e^{-kt} \]

the relationship between values of \( \ln H(t) \) and \( \ln H(t+s) \) is given by the following equation; \( \ln H(t+s) = a + b \cdot \ln H(t) \), where \( t \) is time, \( s \) is a constant time interval of measurements, \( a \) and \( b \) are constants. In the left graph, the horizontal axis represents days and the vertical axis represents measured values. In the right graph, the horizontal axis represents \( \ln H(t) \) and the vertical axis represents \( \ln H(t+1) \). These plots lie along a straight line with a slope of “b” and an intercept of “a”.

Proof:

\[ \ln H(t + s) = \ln G_{\text{max}} - \frac{D_0}{k} + \frac{D_0}{k} e^{-k(t+s)} \]

\[ = \ln G_{\text{max}} - \frac{D_0}{k} + e^{-k} \frac{D_0}{k} e^{-kt} \]

\[ = e^{-k} \left( \ln G_{\text{max}} - \frac{D_0}{k} \right) + e^{-k} \frac{D_0}{k} + \ln G_{\text{max}} - \frac{D_0}{k} + e^{-k} \frac{D_0}{k} e^{-kt} \]

We can substitute that

\[ e^{-ks} = b \] because both are constants.

\[ \therefore \ln H(t + s) = a + b \cdot \ln H(t) \]

Thus, \( \ln H(t+s) \) is a linear function of \( \ln H(t) \) with a slope of \( b \) and an intercept of \( a \).

Here, we can calculate \( k \) value and \( D_0 \) value.

\[ k = -\frac{1}{s} \ln b \]

\[ D_0 = k \left( \ln G_{\text{max}} - \frac{a}{1-b} \right) \]

Where \( \ln G_{\text{max}} \) is equivalent to an initial viral load.

A verification of the model by reviewing published data

i) Telaprevir

Forestier et al. frequently measured HCV viral load in the first 3 days of Telaprevir therapy. After tracing the line on a graph paper, we extracted values of a constant time interval of 0.1 day. When the horizontal axis represents F(t) and the vertical axis represents F(t+0.1), these plots lie along a straight line with a slope of 0.837 and an intercept of 0.505. A correlation coefficient (R²) is 0.998, \( p < 0.0001 \). Actual values were well fit by the calculated equation. (Figure 4, 5, 6)

Figure 4. HCV decline by Telaprevir
exracted values of a constant time interval of 0.1 day (F(t) and F(t+0.1)).

Figure 5. The relationship between F(t+0.1) and F(t)

When the horizontal axis represents F(t) and the vertical axis represents F(t+0.1) of Fig. A4, these plots lie along a straight line with a slope of 0.837 and an intercept of 0.505. A correlation coefficient (R^2) is 0.998, p<0.0001.

Figure 6. Actual value and the calculated equation

Actual values were well fit by the calculated equation.

ii) pegylated interferon alpha with ribavirin (PEG/R)

Data of following figures were retrieved from a recent article about HCV reduction by PEG/R. Likewise, the relationship between F(t) and F(t+7) is a linear function. (Figure 7) Actual values were well fit by the calculated equation. A correlation coefficient (R^2) is 0.996, p<0.0001. (Figure 8)

iii) IFN-β

Asahina et al. reported HCV reduction by IFN-β. Figures represent once a day administration of IFN-β (Figure 9) and twice daily administration (Figure 10). Actual values were well fit by the calculated equation. Note that twice-daily administration resulted in greater reduction of HCV than once a day administration.
When the growth of HCV follows Gomp-Ex model, reduction pattern of HCV is altered according to whether the calculated minimal value (\( \ln H_{\text{min}} \)) is below the Gomp-Ex boundary or not.

Figure 12 Reduction pattern of HCV by applying Gomp-Ex model.

A: When the calculated \( \ln H_{\text{min}} \) is above the Gomp-Ex boundary, Gomp-Ex effect has no influence on the decay curve of \( \ln H(t) = \ln G_{\text{max}} - \frac{D_0}{K} + \frac{D_0}{K} e^{kt} \).

Therefore, an asymptote is same as the calculated \( \ln H_{\text{min}} \).

B: When the calculated \( \ln H_{\text{min}} \) is below the Gomp-Ex boundary, the decay curve becomes straight after it reaches the Gomp-Ex boundary. The slope of the straight line is a summation of the rising slope at the Gomp-Ex boundary and the initial decline slope (-\( D_0 \)). The final slope is also same as the tangent line of the decay curve at which it reaches the Gomp-Ex boundary.

Now we know that the “second phase decline slope” is derived from Gomp-Ex phenomenon.

To reach the Gomp-Ex boundary is essential to achieve eradication of HCV (or tumor cells).

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*This article is a revised and English-translated form of the recent paper, Matsui K. A verification of the assumptive thesis, "HCV kinetics is conformed to Gompertzian model". Kanzo 2009; 50:324-338.
References